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Letter to the editor

Is there rebound psychosis on withdrawal of antipsychotic medication in schizophrenia?

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Letter

Dear Editors:

It is well established that dopamine antagonist medications, antipsychotics, have an important role in the prevention of relapse in schizophrenia and other psychoses (Buchanan et al., 2010; Hasan et al., 2013). Meta-analysis of randomised controlled trials indicates continuation of medication is associated with fewer relapses over the next year than discontinuation (Leucht et al., 2012). However, there remains vigorous ongoing debate around longer-term risks and benefits (Correll et al., 2018), and whether adaptive changes such as dopamine supersensitivity may lead to rebound psychosis on medication withdrawal, which could inflate the apparent benefits of continuing medication (Murray et al., 2016).

Some previous reviews including observational studies have suggested relapse rates are most substantially elevated in the first three months following medication discontinuation, consistent with an early rebound effect. (Baldessarini et al., 1995), analogous with that previously described for lithium withdrawal in bipolar disorder (Suppes et al., 1991). We recently analysed data from randomised trials comparing continuation and discontinuation strategies in people with schizophrenia, using time to event data to allow comparison of effects between different time periods post-randomisation.

Clinical trials in which people with a diagnosis of schizophrenia stable on medication were randomised to either continue on, or withdraw, an antipsychotic medication, were identified from a systematic review reported previously (Leucht et al., 2012). Of these studies the subset presenting time to event data on relapse as survival curves were identified. Survival curve data were extracted using a plot digitizer

(https://automeris.io/WebPlotDigitizer, version 4.1). Interval Hazard Ratios (HR) and their variance were calculated as previously described (Parmar et al., 1998; Tierney et al., 2007). From studies providing data over the first six months following randomisation, pooled estimates of HR and 95% Confidence Intervals (CI) were obtained by inverse variance meta-analysis with a random effects model. Heterogeneity was assessed by use of I^2 . Analyses were performed using *R* (version 3.5), with *meta* package (version 4.9).

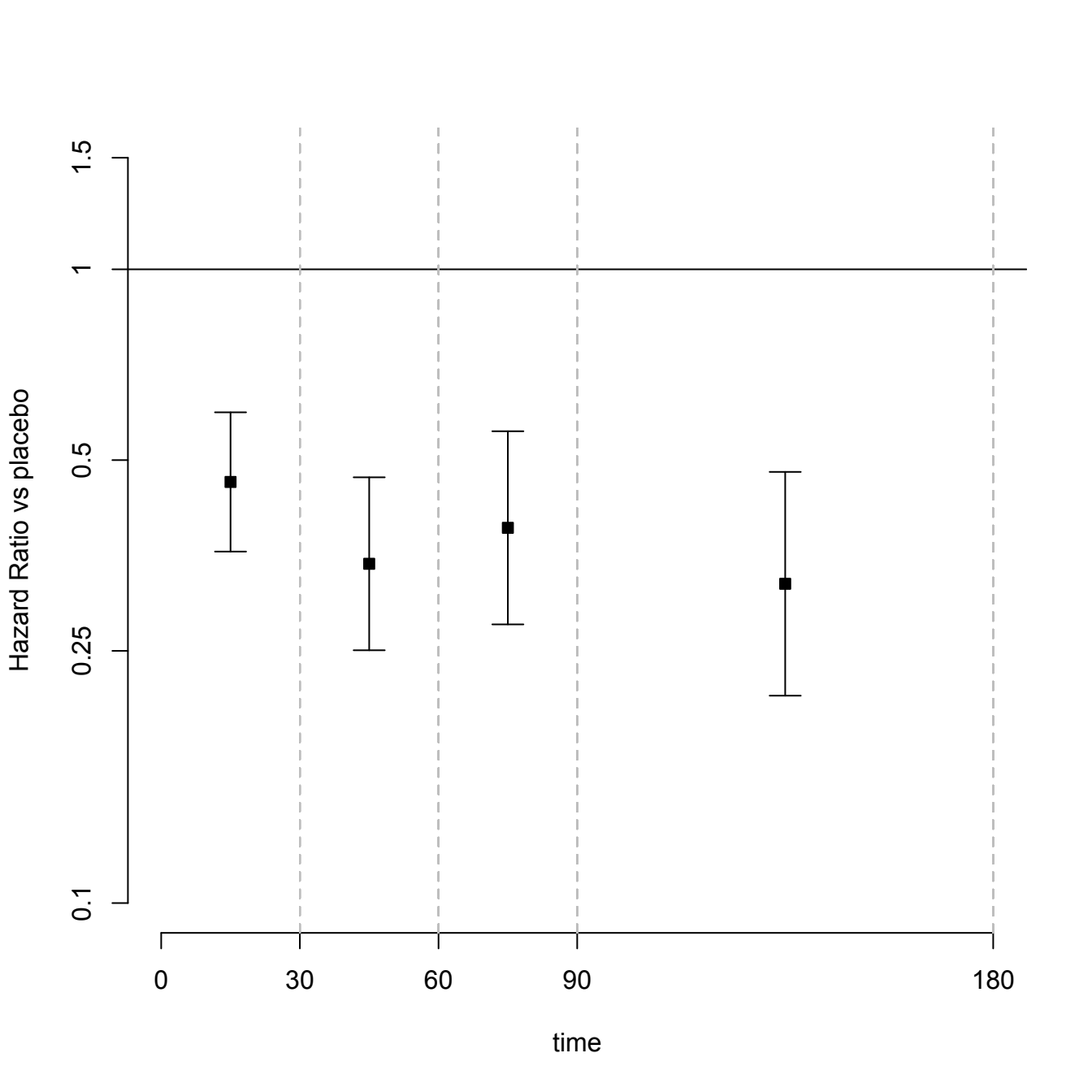
12 randomised controlled trials, in which 2656 participants with schizophrenia had been randomised to continue or discontinue medication, provided survival curve data suitable for analysis over the six month period following randomisation.

Figure 1 near here

People continuing antipsychotic medication were at lower risk of relapse over the six months following randomization - HR 0.38 (95% CI 0.32 to 0.44). A similar effect was seen across times studied (Figure 1). There was no significant effect of time on HR (p=.3). Within the first month after randomisation, HR 0.46 (95% CI 0.36 to 0.59).

These data from meta-analysis of randomised controlled trials confirm a lower risk of relapse in those randomised to continue antipsychotic medications. HRs within the first six months are similar to the overall estimates of risk ratio (0·40, 95% CI 0·33 to 0·49) previously described (Leucht et al., 2012). Contrary to previous reports (Baldessarini et al., 1995), no evidence of excess early relapse in those stopping medication was seen - the consistent hazard ratio over time indicates no general early rebound phenomenon is seen, although a specific effect of particular agents, or in particular populations, cannot be excluded by this overall analysis. Future studies could specifically investigate those treated with clozapine, treatment-resistant

schizophrenia, where apparent rebound is most often suspected (Chouinard et al., 2017).


Hazard Ratio vs placebo
1.5
1
0.5
0.25
0.1
0
30
60
90
180
time

Legends

Figure 1

Risk of relapse (Hazard ratios with 95% Confidence Intervals) over time following randomisation (days) between continuation and discontinuation of antipsychotic medication in people with schizophrenia (*k* = 12 trials, *n* = 2656 participants). Vertical dashed lines mark the boundaries of time intervals over which effect estimates were made.

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